PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CZ2004/000078	23.11.2004	25.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/58, A61K9/28, A61K9/20, A61K9/48

Applicant
PLIVA-LACHEMA A.S.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CZ2004/000078

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5, 7
	No:	Claims	1-4, 6
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	5, 7
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	-

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/CZ2004/000078

V Reasoned statement under Rule 66.2 (a) (ii) with regard to novelty, inventive step or industrial applicability

1) Clarity

1.1) Claims 1/ 2-7 in part are product-by-process claims, hence not rendering a product novel by the fact that it is produced by means of a new process. Where a claim defines a product in terms of the process by which the product is made, the claim as a whole is directed to a product (PCT International Search and Preliminary Examination Guidelines. 5.26. March 25th, 2004; Article 6 PCT).
The claim defining a product in terms of a process is to be construed as a claim to the product as such, namely with expressions such as "Product X obtainable by process Y".

1.2) Example 3 does not specify exactly enough according to which directions and with which type of apparatuses the dissolution test is to be carried out. The reference to a commonly known and acknowledged pharmacopoeia would have increased the clarity for said investigation (Article 6 PCT).

2) Documents
The following documents (D1-D4) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 99/08684 A (GLAXO GROUP LIMITED; PARR, ALAN, FRANK; RIZZOLIO, MICHELE, CATHERINE) 25 February 1999 (1999-02-25)
D2: US 6 294 192 B1 (PATEL MAHESH V ET AL) 25 September 2001 (2001-09-25)
D3: US 2003/064097 A1 (PATEL MAHESH V ET AL) 3 April 2003 (2003-04-03)

Unless otherwise specified, reference is made to the respective cited passages in D1-D4 (see the International Search Report, Form PCT/ISA/210).

3) Novelty - Article 33 (1) and (2) PCT

3.1) D1 discloses a pharmaceutical composition in form of a capsule which contains a solution comprising the following components: a pharmaceutically active aza steroid (preferred finasteride), polyethylene glycol, propylene glycol and a surfactant which includes sodium dodecyl sulfate besides polysorbate 80, docusate sodium. The additional function of a lubricant for polyethylene glycol or sodium lauryl sulfate is not to be ruled out.
With D2 a pharmaceutical composition for tablets or capsules is described based on a solid carrier which contains a substrate and an encapsulation coat on the substrate, wherein the encapsulation coat comprises at least one pharmaceutical active ingredient (finasteride besides others) and at least one hydrophilic surfactant, where an anionic surfactant, such as sodium lauryl sulphate, is preferred.
Comparably to D2, D3 focusses on a capsule for oral administration comprising a hydrophobic therapeutic agent which may be finasteride besides others, and a carrier which contains at least one hydrophobic surfactant and at least one hydrophilic surfactant. Herewith anionic surfactants, such as sodium lauryl sulphate, are preferred.

In D1-D3, for one component a preferred agent is given which corresponds to that in present application. Therefore selections have to be made only out of one list.
Milling and spraying are mentioned as steps of manufacturing in D2 as well as D3.
Sorbitol, mannitol and cellulose derivatives are used as solubilizers, the additional lubricating properties of sodium lauryl sulfate can be assumed in D2 and D3.

3.2) In the light of D1-D3 (see sections V-2, 3.1) and under consideration of section V-1.1, 1.2, the subject-matter of claims 1-4, 6 is considered not novel according to Article 33 (1) and (2) PCT. In particular, the composition claimed does not seem to be novel, the manufacturing process itself cannot thus render this composition novel (see V-1.1).

3.3) Consequently, - under consideration of V-1.1, 1.2 - the subject-matter of claims 1-4, 6 appears to be novel (Article 33 (1), (2) PCT), since its corresponding content is not disclosed by D1-D3.

4) Inventive Step - Article 33 (1) and (3) PCT

4.1) The problem posed in the present application was a finasteride solid dosage formulation with an instant release of the active agent enabling finasteride processing to the dosage form irrespectively of the size of its particles, i.e. also large finasteride particles.

The solution according to the Applicant was a pharmaceutical composition comprising finasteride (in an aqueous suspension!) and an anionic surfactant, the manufacturing included milling and spraying into a fluid bed.

D1 which is regarded closest prior art discloses a pharmaceutical composition in form of a capsule which contains a solution comprising the following components: a pharmaceutically active aza steroid (preferred finasteride), polyethylene glycol, propylene glycol and a surfactant which includes sodium dodecyl sulfate besides polysorbate 80, docusate sodium.

D1 does not disclose steps of manufacturing, film-coated tablets as presentation and the use of disintegrants.

Unexpected or surprising effects do not seem to be connected with the manner of manufacturing or with the coating of the tablets or with the use of disintegrants.

4.2) Therefore, under provision of V-1.1, 1.2, the subject-matter of claims 5, 7 is obvious to a person skilled in the art due to the common textbook knowledge and galenical experience. Thus the aforementioned subject-matter does not meet the requirements of Article 33 (1) and (3) PCT in that extent that it cannot be considered inventive.

5) Certain documents cited
On the basis of rule 70.10 PCT certain published documents - namely those published after filing /priority date of present application (Rule 64 (3) PCT) - should be mentioned as such. This refers to D4

demonstrating the following details:

Application No: PCT/IS2003/000034
Patent No: WO2004/047798
Publication date: 10.06.2004
Filing date: 21.11.2003
Priority date: 22.11.2002

D4 discloses a pharmaceutical composition in form of a tablet which comprises 0.1-10 wt % of finasteride, 0-10 wt% of sodium lauryl sulfate (as a wetting agent) and 0-90 wt% of microcrystalline cellulose. Tablets are manufactured using wet granulation.

6) Further remarks
The Applicant's attention is drawn to the fact that the application must not be altered thus that its subject-matter might exceed the contents of the application originally filed (Article 41 (2) PCT).

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Law and Patent Offices

Patents, Trademarks, Designs, Licences

Prague, July 15, 2005

International Bureau of WIPO
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Re: Applicant's comments on Written Opinion
Your ref.: PCT/CZ2004/000078
Our ref.: 150387/KB

This is to the Written opinion as issued by the International Searching Authority (further as ISA, only).

First of all, the Applicant opposes to the ISA's allegation qualifying the present claims 1 to 7 to be product-by-process claims. There is, in fact, no endeavor of the Applicant to obtain a direct product patent protection for the oral solid dosage form as produced by the process disclosed in the present patent application (further as "invention process", only) imposing said form as a novel product. Unlike this, the Applicant's effort is restricted to obtain the process protection for his novel process of preparing said oral solid dosage form. No matter whether this dosage form is novel or not. Accordingly, the whole language of the present main claim, inclusive of the preamble to it, is properly process one not including but process features. The same goes for the other present dependent process claims. The Applicant is of the opinion that if both the novelty and inventiveness of the invention process are ascertained the invention process should only be compared with relating prior art processes, i.e.. with those deductible from D1 to D4 in the given case.

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The invention process consists substantially in 1) **milling an aqueous suspension of finasteride and an anion surfactant** to a specific particle size distribution and 2) **spraying the obtained fine suspension in a fluid bed onto a solid particle hydrophilic carrier** having a specific particle size distribution. The spirit of the present invention is thus based on the novel and inventive genuine discovery of that the presence of the surfactant gives the following double profit: firstly, the surfactant makes possible micronization of finasteride being, on its own, later beneficial for releasing finasteride from the oral solid dosage form and secondly, i.e. after spraying onto the hydrophilic carrier, the surfactant further promotes said release of finasteride from the oral solid dosage form. The above mentioned invention combination of the both principal steps (milling/spraying) is neither described nor suggested anywhere in D1 to D4. Such a combination thus could not be deductible by the skilled person in obvious way from D1 to D4, either.

A1) Novelty of the invention process in view of D1 (**WO 99/08684**)

D1 concerns a solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid (finasteride, for instance), polyethylene glycol and propylene glycol intended to be encapsulated and prepared by simply progressively mixing all said components (see the bridging paragraph of pages 10/11 of D1). At the first sight, it is evident that the matter as comprised in D1 is conceived and realized far away from the invention process. No invention combination milling/spraying is neither mentioned nor hinted in D1 as a result of which the invention process should be considered novel against the content of D1.

A2) Novelty of the invention process in view of D2 (**US 6,294,192 B1**)

The solution of D2 is based on that the compositions including a combination of a hydrophilic surfactant and a hydrophobic surfactant can solubilize therapeutically effective amounts of hydrophobic therapeutic agents (inclusive of finasteride) without recourse to use of

triglycerides (see lines 54-58 of col. 4 of D2). It ensues from Example 1 of D2 (see bridging paragraph of columns 31/32 of D2), that the concerned composition also is prepared by a mere progressively mixing all the composition components rather than by using the invention combination milling/spraying. The true is, claim 73 of D2 discloses a multiparticulate dosing form comprised of a plurality of beads each coated by said composition but nowhere in D2 is set forth that this form is prepared by spraying an aqueous suspension of the mentioned components onto said beads let alone by spraying the suspension obtained after preceding milling of the active ingredient in the presence of the anion surfactant being the same as used while immediately after spraying. For these reasons, the invention process should be considered novel against the content of D2.

3A) Novelty of the invention process in view of D3 (**US 2003/0064097 A1**)

D3 provides a pharmaceutical composition comprising a solid carrier, the solid carrier comprising a substrate and an encapsulation coat on the substrate, wherein the encapsulation coat comprises at least one pharmaceutical active ingredient (inclusive of finasteride) and at least one hydrophilic surfactant. The fact is, this composition can be prepared by spraying a suspension of the components of the encapsulation coat in an aqueous medium (see paragraph [0224] of D3) in a fluid bed (see paragraph [0223] of D3) onto the substrate (which can be sugar beads, for instance; see paragraph [0287] of D2) but nowhere throughout D3 is neither mentioned nor hinted that the suspension as sprayed was obtained by milling the active ingredient to a specific particle size distribution in the presence of the same anion surfactant as only present during spraying the micronized active ingredient onto the solid particle hydrophilic carrier having a specifical particle size distribution, as well. For this reason, the invention process should be regarded as novel against the content of D3.

4A) Novelty of the invention process in view of D4 (**WO 2004/047798 A2**)

D4 describes a solid tablet pharmaceutical formulation

comprising finasteride, wetting agent (sodium lauryl sulfate, for instance) and microcrystalline cellulose, optionally in combination with other excipients. Taking into account that this formulation is prepared by wet granulation (see Examples of D4) as opposed to the invention combination milling/spraying the invention process should be considered novel over the process of D4.

B) The inventiveness of the invention process in view of D1 to D4

According to all the prior art documents as objected by ISA the improved delivery of hydrophobic therapeutical agents (inclusive of finasteride) from solid drug forms is reached by adding surfactant to the hydrophobic therapeutical agents either via mere mixing or spraying an aqueous suspension of the hydrophobic therapeutical agents in a fluid bed onto a particulate carrier. Over this prior art concept, the invention process comes with an original idea to use such surfactant, immediately before spraying a mixture thereof with a hydrophobic therapeutical agent in an aqueous medium onto a particulate carrier, to enable the preceding micronization of the hydrophobic therapeutical agent via milling the mentioned mixture. Nowhere in the documents D1 to D4 is any hint that would have motivated the skilled person to take this approach for further promote the release of finasteride from the solid drug form. The invention process in fact makes possible to very simply combine, for finasteride, two so far separately used strategies (micronization and surfactant ones) into a compact process by finding out a link between them including the specific process conditions as defined in claim 1 of the present application. Taking into account the foregoing the Applicant is of the opinion the invention process should be considered inventive over the content of D1 to D4.

The Applicant´s argumentation as given above concerns more or less claim 1. As far as the other dependent process claims 2 to 7 are concerned, the rules stipulate both the novelty and inventiveness of dependent claims should not be ascertained but in a combination with the claim from which the dependent claims derive. Once claim 1 of the present

application being considered novel (as displayed above) novel should also be the combinations thereof with the dependent claims 2 to 6, respectively. Claims 2 to 7 should be considered inventive, as well, since they specifically relate to the obligatory conditions of claim 1.

Regarding Example 3 of the present application allegedly lacking indication concerning the apparatuses used for the dissolution test, the Applicant completes the dissolution test of Example 3 was implemented under the conditions of paddle method USP II (in 900 ml of purified and degasified water at 37°C and 50 rpm; "off-line HPLC method). The Applicant is prepared to complete Example 3 in this sense as soon as he is enabled by rules to proceed so.

While elaborating the comments on the Written opinion the Applicant detected a typographical error in the English version of the present application. The thing is line 8 of claim 1 (page 8) presently reads: "aqueous suspension is sprayed **to** a fluid bed onto a solid particle hydrophilic carrier having" whereas it should correctly read: "aqueous suspension is sprayed **in** a fluid bed onto a solid particle hydrophilic carrier having" as it is consistent with the wording of claims 4 to 6 where the specification "**in** the fluid bed" is used. The same error is repeated in line 9 of page 3 and in line 11 of page 10, yet. To set the concerned text right, the Applicant submits herewith new amended pages 3, 8 and 10 as substitute sheets.

On behalf of
PLIVA-LACHEMA A.S.

Jan Kubát
European patent attorney

Encl.: substitute sheets 3,8,10